

## ORIGINAL RESEARCH

# Prospective Case-Control Study of Cardiovascular Abnormalities 6 Months Following Mild COVID-19 in Healthcare Workers



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## ABSTRACT

**OBJECTIVES** The purpose of this study was to detect cardiovascular changes after mild severe acute respiratory syndrome-coronavirus-2 infection.

**BACKGROUND** Concern exists that mild coronavirus disease 2019 may cause myocardial and vascular disease.

**METHODS** Participants were recruited from COVIDsortium, a 3-hospital prospective study of 731 health care workers who underwent first-wave weekly symptom, polymerase chain reaction, and serology assessment over 4 months, with seroconversion in 21.5% (n = 157). At 6 months post-infection, 74 seropositive and 75 age-, sex-, and ethnicity-matched seronegative control subjects were recruited for cardiovascular phenotyping (comprehensive phantom-calibrated cardiovascular magnetic resonance and blood biomarkers). Analysis was blinded, using objective artificial intelligence analytics where available.

**RESULTS** A total of 149 subjects (mean age 37 years, range 18 to 63 years, 58% women) were recruited. Seropositive infections had been mild with case definition, noncase definition, and asymptomatic disease in 45 (61%), 18 (24%), and 11 (15%), respectively, with 1 person hospitalized (for 2 days). Between seropositive and seronegative groups, there were no differences in cardiac structure (left ventricular volumes, mass, atrial area), function (ejection fraction, global longitudinal shortening, aortic distensibility), tissue characterization (T<sub>1</sub>, T<sub>2</sub>, extracellular volume fraction mapping, late gadolinium enhancement) or biomarkers (troponin, N-terminal pro-B-type natriuretic peptide). With abnormal defined by the 75 seronegatives (2 SDs from mean, e.g., ejection fraction <54%, septal T<sub>1</sub> >1,072 ms, septal T<sub>2</sub> >52.4 ms), individuals had abnormalities including reduced ejection fraction (n = 2, minimum 50%), T<sub>1</sub> elevation (n = 6), T<sub>2</sub> elevation (n = 9), late gadolinium enhancement (n = 13, median 1%, max 5% of myocardium), biomarker elevation (borderline troponin elevation in 4; all N-terminal pro-B-type natriuretic peptide normal). These were distributed equally between seropositive and seronegative individuals.

**CONCLUSIONS** Cardiovascular abnormalities are no more common in seropositive versus seronegative otherwise healthy, workforce representative individuals 6 months post-mild severe acute respiratory syndrome-coronavirus-2 infection. (J Am Coll Cardiol Img 2021;14:2155–2166) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## ABBREVIATIONS AND ACRONYMS

**CMR** = cardiovascular magnetic resonance

**COVID-19** = coronavirus disease-2019

**hsTnT** = high-sensitivity troponin T

**LGE** = late gadolinium enhancement

**LV** = left ventricular

**NT-proBNP** = N-terminal pro-B-type natriuretic peptide

**SARS-CoV-2** = severe acute respiratory syndrome-coronavirus-2

The coronavirus disease-2019 (COVID-19) pandemic caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has variable clinical impact. The majority of cases are mild and often asymptomatic, but a minority of individuals have severe acute respiratory syndrome, the most frequent cause of death (1). Multiorgan involvement occurs in severe disease, and the cardiovascular system is often involved in hospitalized COVID-19. Mechanisms include acute coronary syndrome, exacerbation of pre-existing cardiovascular disease, arrhythmia, myocarditis, and microangiopathic thrombosis (2). Pathophysiological mechanisms include disordered clotting,

superimposed infection, cytokine storm, and hemophagocytic lymphohistiocytosis (3,4). Troponin elevation is common in severely ill hospitalized patients (5) and associated with adverse outcomes (6). However, cardiovascular disease is also a known risk factor for severe disease (7), so disentangling association and causation is challenging.

Cardiovascular magnetic resonance (CMR) has proven utility for diagnosis in patients with elevated troponin from unclear causes (8,9) by measuring cardiac structure, function, myocardial scar (late gadolinium enhancement), and edema ( $T_1$  and  $T_2$  mapping). Despite the logistical challenges of CMR during acute severe hospitalized COVID-19, studies reported multiple CMR abnormalities in these patients (10,11).

During convalescence, long-term cardiovascular effects and their (12) mechanisms are currently unclear, but chronic myocarditis has been proposed following severe hospitalized COVID-19 (13). Recent CMR studies have reported cardiac abnormalities after COVID-19 in up to 78% of patients, even after

mild, nonhospitalized illness with evidence of ongoing myocardial inflammation in 60% (14). Such a prevalence of chronic myocarditis after mild disease has prompted societal concerns in diverse domains and suggests that screening should be considered post-COVID-19, even in asymptomatic individuals. However, study design issues (mixed severe and mild patients, historic control subjects, CMR sequence choice, and the definition of normal for mapping), concern that an isolated elevation of a parameter such as  $T_1$  or  $T_2$  is not disease, and errors requiring post-publication revision (15) have stimulated further investigation, with particular focus on mild disease. Furthermore, autopsy studies have suggested that myocarditis may not be as common as initially thought (16).

We therefore aimed to determine the prevalence and extent of late cardiac and cardiovascular sequelae after mild nonhospitalized SARS-CoV-2 infection.

## METHODS

This was a nested case-control study within COVID-sortium (ethical approval: South Central-Oxford A Committee, 20/SC/0149, [NCT04318314](#); diffuse fibrosis CMR ethics: 07/H0715/101). Details have been previously described (17). In brief, the parent COVID-sortium study is a prospective study of 731 health care workers from 3 London hospitals starting early in the first COVID-19 wave. Participants underwent serial weekly polymerase chain reaction (PCR) and serology testing over 16 weeks ( $n = 6,495$  Roche cobas, SARS-CoV-2 PCR;  $n = 12,990$  Eurimmun anti spike S1 and Roche anti nucleocapsid tests [Roche, Basel, Switzerland]), with symptom ascertainment (median 10 visits). Comorbidities were relatively low (18% smokers, 13% body mass index  $>30$  kg/m<sup>2</sup>, 11% asthma, 7% hypertension, 2% diabetes, 1%

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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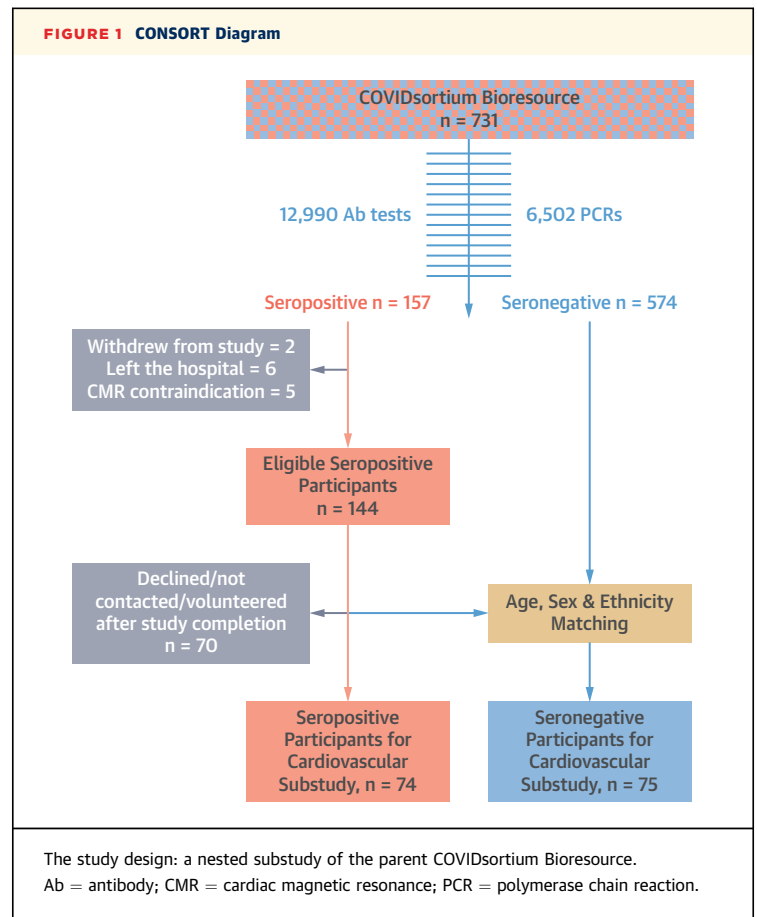
rheumatological disease, 1% cancer). A total of 38% were non-White, including 6% of Black ethnicity). Across the overall study, 21% (n = 157) seroconverted. Disease was mild in 99%, with 25% asymptomatic and only 2 hospitalized (2 days, no deaths). All infections occurred prior to May 1, 2020 (no new seroconversions, no new PCR-positive tests), with more than 90% of infections understood (from PCR, symptoms, and antibody data) to have been between March 1, 2020, and April 14, 2020 (18,19).

**PARTICIPANTS.** Participants were invited to the cardiovascular nested substudy. In total, 74 seropositive participants (47% of total seropositive patients; 51% of available seropositive patients [2 withdrew, 6 left the hospital, and 5 had CMR contraindications (2 pregnancy, 1 implant, 1 metallic fragment, and 1 prior contrast reaction)]) were recruited, along with 75 age-, sex-, and ethnicity-matched control subjects selected from volunteering seronegative subjects. Control subjects were recruited blinded to clinical data.

**STUDY PROTOCOL.** Blood was taken for cardiac biomarkers (high-sensitivity troponin T [hsTnT] and N-terminal pro-B-type natriuretic peptide [NT-proBNP]) and hematocrit. Peripheral and central blood pressures were recorded as the average of suprasystolic oscillometric blood pressure measurements acquired over 10 s at 200 Hz in duplicate after a period of rest in the semisupine position, as per international guidelines (Cardioscope II BP+, Uscom Ltd., Sydney, Australia).

**CARDIAC MAGNETIC RESONANCE.** Scans were acquired at 2 sites: Royal Free (1 scanner) or Barts (2 scanners) between September 3, 2020, and November 7, 2020, in accordance with infection control guidelines (20) on 1.5-T CMR scanners (Magnetom Aera, Siemens Healthcare, Erlangen, Germany). Given pandemic pressures, an adapted 30-min protocol was used. This comprised anatomic images, long- and short-axis cines, T<sub>1</sub>, T<sub>2</sub>, and extracellular volume fraction (ECV) mapping (a mid-short axis and 4-chamber view each) with late gadolinium enhancement and aortic pulse wave velocity. T<sub>1</sub> mapping used a modified Look-Locker inversion recovery sequence (5s[3s]3s pre-contrast, 4s[1s]3s[1s]2s post-contrast). The contrast was 0.1 mmol/kg Gadoterate meglumine (gadolinium-DOTA, Dotarem, Guerbet S.A., Paris, France). Mapping acquisition/analysis followed international consensus statements (21,22) with additional quality assurance steps as indicated in the Supplemental Appendix.

**CMR ANALYSIS.** All quantitative analyses were performed blinded to participant status. All scans were initially clinically reported (J.C.M.) and significant



incidental extracardiac/cardiac findings and blood test abnormalities were committee adjudicated (J.C.M., C.M., T.A.T.) with appropriate action as needed (further testing, clinical review). Left ventricular (LV) structure and function was analyzed using a clinically validated artificial intelligence (AI) platform (23). Left atrial (LA) area and global longitudinal shortening was analyzed by further validated AI approaches (Supplemental Methods) (24). Aortic stiffness, distensibility, and pulse wave velocity were measured using validated software (ArtFun+, Imageens, Paris, France) and central pulse pressure. A standard operating procedure was developed for T<sub>1</sub>, T<sub>2</sub>, ECV, and late gadolinium enhancement (LGE), with all analyses performed by 2 observers (GJ and RA) using Circle CVI42 version 5.12.1 (Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada). Quality assurance procedures included review of motion correction, artifact review, the use of field maps for potential bias errors, and a blinded contour review by an independent U.S.-based team for technical errors (P.K.), and clinical plausibility (E.B.S.). In brief, endocardial and epicardial contours (10% offset) were drawn and automatically divided into 6 segments. For LGE, a 3-SD approach was taken. LGE

**TABLE 1 Cohort Characteristics**

	Whole Cohort (N = 149)	Seropositive (n = 74)	Seronegative (n = 75)	p Value
<b>Demographics</b>				
Age, yrs	37 (31–48)	39 (30–48)	37 (31–47)	0.89
Female	86 (58)	46 (62)	40 (53)	0.28
BSA, m <sup>2</sup>	1.89 ± 0.22	1.88 ± 0.21	1.90 ± 0.23	0.51
<b>Ethnicity</b>				
White	103 (69)	50 (68)	53 (71)	0.68
Black	17 (11)	10 (14)	7 (9)	0.42
Asian	20 (13)	11 (15)	9 (12)	0.61
Mixed race	9 (6)	3 (4)	6 (8)	0.49
<b>Role</b>				
Doctor	40 (27)	20 (27)	20 (27)	0.96
Nurse	48 (32)	25 (34)	23 (31)	0.68
Ancillary staff	53 (36)	26 (35)	27 (36)	0.91
Other	8 (5)	3 (4)	5 (7)	0.71
<b>Past medical history</b>				
Hypertension	14 (9)	10 (14)	4 (5)	0.09
Hyperlipidemia	7 (5)	4 (5)	3 (4)	0.69
Diabetes mellitus	3 (2)	2 (3)	1 (1)	0.62
Smoker (previous or current)	24 (16)	10 (14)	14 (19)	0.39
Family history of CAD	21 (14)	9 (12)	12 (16)	0.5
Asthma/COPD	18 (12)	13 (17)	5 (7)	0.04
Exercise, h/week	3.5 (2.0–5.0)	3.5 (2.0–5.0)	3 (1.5–6.0)	0.84
<b>Symptoms</b>				
Asymptomatic		11 (15)		
Noncase definition <sup>a</sup>		18 (24)		
Case definition <sup>a</sup>		45 (61)		

Values are median (interquartile range), n (%), or mean ± SD. <sup>a</sup>Case definition—at least one of the following (fever, cough, shortness of breath, anosmia, ageusia, or dysgeusia).  
BSA = body surface area; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease;

of <1% of the myocardium at the right ventricular (RV) insertion points only was ignored. ECV was derived using a same-day hematocrit. Magnet quality assurance used the T1MES phantom to ensure no differences between the 3 magnets and no temporal drift (25,26). Across the 3 magnets, temperature-corrected T<sub>1</sub> and T<sub>2</sub> was within 0.33% and 0.95%, respectively, with temporal drift of <1% (Supplemental Methods).

**POWER CALCULATION.** For information about power calculations, please see the Supplemental Methods.

**STATISTICAL ANALYSIS.** Analyses were prespecified. The 5 primary analyses were LV ejection fraction (EF), indexed end-diastolic volume, percentage LGE, septal T<sub>1</sub>, and septal T<sub>2</sub>. The 5 secondary analyses were indexed LV mass, indexed LA area, global longitudinal shortening (average of 3 views), septal ECV, and aortic distensibility (diaphragm level). Planned exploratory analyses were global and segmental mapping, heart rate, NT-proBNP and hsTnT levels, and blood pressure. Correlations of any

SARS-CoV-2-associated cardiovascular abnormalities were planned with: 1) demographics; 2) immune response (peak antibody); and 3) symptoms (case defining, noncase defining, asymptomatic).

Analyses used SPSS Statistics version 26 (IBM, Armonk, New York). Data were examined for normality using the Kolmogorov-Smirnov test and visual inspection of histograms and Q-Q plots. Normally distributed variables were expressed as mean ± SD; non-normal as median (interquartile range [IQR]). Proportions were expressed as absolute frequencies and percentages. Independent and paired Student's tests (2-tailed), the Mann-Whitney U test, Wilcoxon signed-rank test, and chi-square and Fisher exact test were used as appropriate. The 5 primary and 5 secondary endpoints were to be considered separately, with each having a critical 2-sided Benjamini-Hochberg's p value to be considered significant, assuming a false discovery rate of 5%.

**DATA ACCESS.** All individual participant deidentified data (serology, PCR results, Digital Imaging and Communications in Medicine images, meta-data, data dictionaries) are available upon reasonable request (Supplemental Methods).

## RESULTS

**PATIENTS.** The study CONSORT diagram is shown in Figure 1. A total of 149 subjects (74 seropositive vs. 75 seronegative; median age 37 years [range 18 to 63 years], 42% men, 32% non-White ethnicity) were recruited from COVIDsortium and underwent cardiovascular phenotyping 6 months 9 days (IQR: 5 months 26 days to 6 months 20 days) post-SARS-CoV-2 infection. Cases were well matched (Table 1).

Seropositive infections had been mild with case definition symptoms (fever, new dry cough, anosmia, ageusia, or dysgeusia), noncase definition symptoms, and asymptomatic disease in 45 (61%), 18 (24%) and 11 (15%) respectively, with 1 person hospitalized (for 2 days). Symptoms had been recorded throughout the parent study weekly. At the time of scanning (6 months), 16 (11%) reported symptoms: 5 (3%) sore throat; 4 (3%) fatigue; 4 (3%) rhinorrhea; 3 (2%) shortness of breath; and 1 (1%) each of productive cough, chills, diarrhea, anosmia, and ageusia, with no difference between seropositive and seronegative subjects (6 [8%] vs. 10 [13%]; p = 0.47).

**STUDY.** CMR scanning took a median 30 min (IQR: 27 to 32 min). Example images and the CMR protocol are shown in Supplemental Figure 1. All data were >99% complete (see details in the Supplemental Methods). Segmentation of LV structure, function, LGE, T<sub>1</sub>, and T<sub>2</sub> are shown in Supplemental Figure 2.

**TABLE 2 Primary and Secondary Analyses Results**

	Whole Cohort (N = 149)	Seropositive (n = 74)	Seronegative (n = 75)	p Value
<b>Blood pressure</b>				
Peripheral sBP, mm Hg	119 (109–130)	115 (109–130)	121 (110–131)	0.3
Peripheral dBP, mm Hg	75 ± 9	74 ± 9	75 ± 10	0.58
<b>Laboratory investigations</b>				
Hs troponin T (normal <14)	4 (3–7)	4 (3–7)	4 (3–7)	0.57
NT-proBNP (normal <400)	31 (18–54)	36 (18–53)	28 (17–56)	0.24
<b>Function</b>				
LVEF, %	67.1 (63.7–70.1)	67.5 (64.4–70.2)	66.8 (62.8–70.1)	0.28*
GLS mean, %	17.4 ± 2.1	17.5 ± 1.8	17.3 ± 2.4	0.62†
<b>Structure</b>				
LVEDV indexed, ml/m <sup>2</sup>	78.8 (70.2–90.9)	78.1 (69.7–90.3)	80.0 (71.3–94.9)	0.37*
LA area indexed, ml/m <sup>2</sup>	12.0 (10.9–13.1)	12.0 (11.0–13.2)	11.9 (10.6–13.1)	0.87†
LV mass index, g/m <sup>2</sup>	46.6 (41.2–56.7)	47.5 (41.5–57.6)	47.5 (41.5–56.7)	0.56†
<b>Tissue characterization</b>				
LGE, %	0.29 ± 0.86	0.27 ± 0.78	0.32 ± 0.93	0.72*
RV insertion point	14 (9)	8 (11)	6 (8)	0.56
Non-RV insertion point	13 (9)	6 (8)	7 (9)	0.79
T1 septum, ms	1,018 ± 31	1,020 ± 34	1,016 ± 28	0.42*
High	6 (4)	5 (7)	1 (1)	0.12
T1 global, ms	1,009 ± 27	1,010 ± 28	1,007 ± 25	0.47
High	6 (4)	4 (5)	2 (3)	0.44
T2 septum, ms	48.7 ± 2.2	48.8 ± 2.5	48.6 ± 1.9	0.63*
High	9 (6)	7 (9)	2 (3)	0.098
T2 global, ms	48.6 ± 1.9	48.7 ± 1.9	48.4 ± 1.9	0.3
High	7 (5)	4 (5)	3 (4)	0.72
ECV septal, %	22.2 ± 2.1	22.3 ± 2.0	22.1 ± 2.2	0.57†
High	5 (3)	3 (4)	2 (3)	0.68
ECV global, %	21.5 ± 2.0	21.6 ± 1.9	21.5 ± 2.1	0.73
High	4 (3)	3 (4)	1 (1)	0.37
<b>Aortic stiffness</b>				
Distensibility, mmHg <sup>-1</sup> ·10 <sup>-3</sup>	12.3 (8.7–17.5)	12.6 (9.1–18.3)	12.0 (8.7–17.1)	0.74†

Values are median (interquartile range), mean ± SD, or n (%). NT-proBNP in pg/ml and hs-troponin T in ng/ml. All indexing is to body surface area. \*Pre-specified primary endpoint. †Pre-specified secondary endpoint.

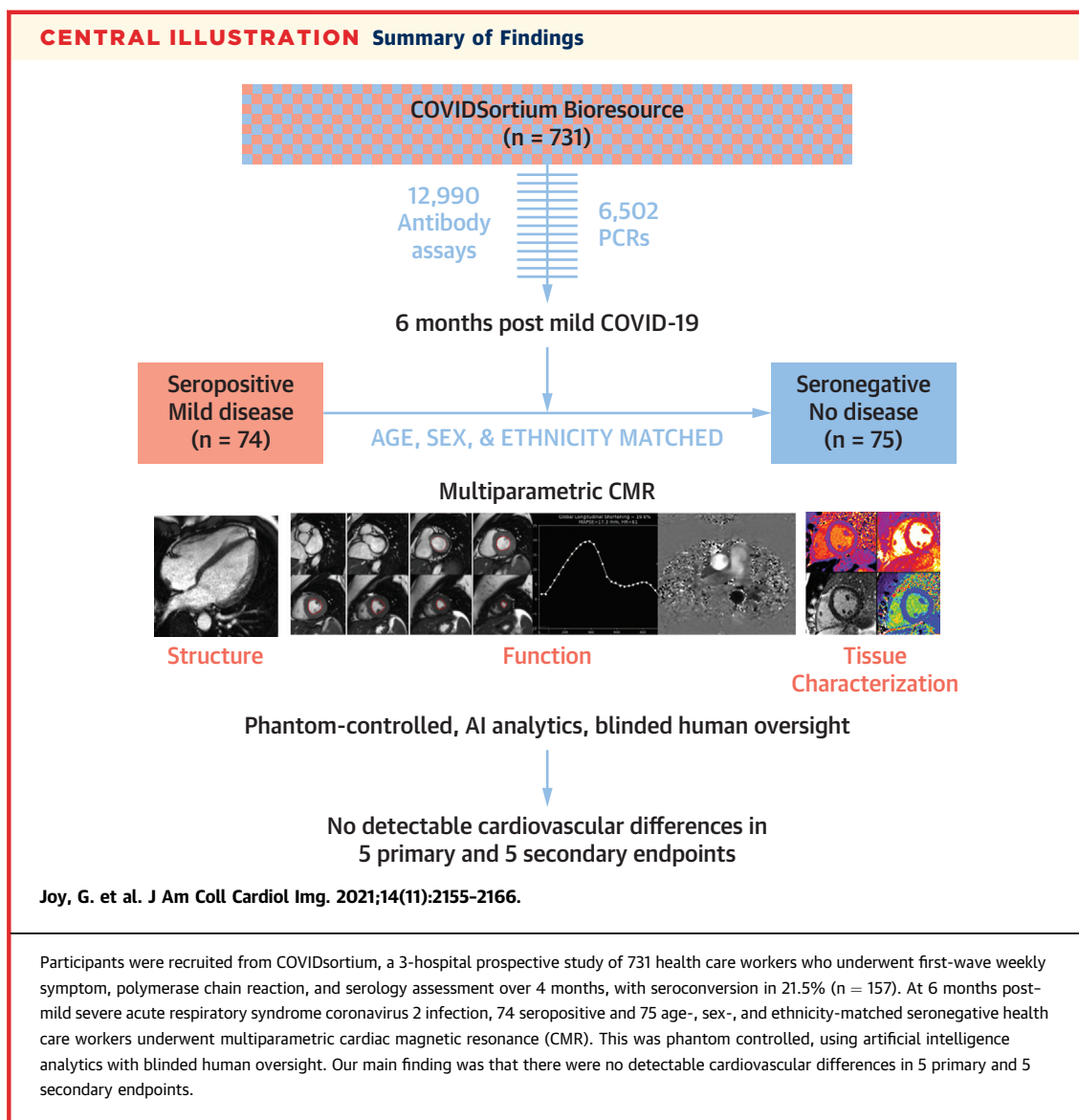
BSA = body surface area; COPD = chronic obstructive pulmonary disease; dBP = diastolic blood pressure; ECV = extracellular volume fraction; EDV = end-diastolic volume; EF = ejection fraction; GLS = global longitudinal shortening; IQR = interquartile range; LGE = late gadolinium enhancement; LV = left ventricle; LVM = left ventricular mass; NT-proBNP = N-terminal pro-brain natriuretic peptide; RV = right ventricular; sBP = systolic blood pressure.

**PRIMARY AND SECONDARY ENDPOINTS.** Between seropositive and seronegative groups, there were no statistically significant differences in any of the 5 pre-specified primary endpoints (LVEF, indexed end-diastolic volume, LGE%, septal T<sub>1</sub>, septal T<sub>2</sub>, marked as dagger in Table 2) or 5 pre-specified secondary endpoints (LV mass indexed, LA area indexed, global longitudinal shortening [average of 3 views], septal ECV, and aortic distensibility marked as double daggers in Table 2), even without correction for multiple testing (Benjamini-Hochberg's method), with all p values >0.05 (Central Illustration). All other comparisons were also nonsignificant (Table 2). Between-group differences between T<sub>1</sub> and T<sub>2</sub> are shown in Figure 2.

**ADDITIONAL ENDPOINTS.** There were no between-group differences (seropositive vs. seronegative) across any exploratory analyses, including global

(rather than septal) T<sub>1</sub>, T<sub>2</sub> or ECV, RV volumes or RVEF, ascending and descending thoracic aortic pulse wave velocity, heart rate, NT-proBNP, hsTnT, or blood pressure. As no CMR or biomarker abnormalities were associated with prior SARS-CoV-2 infection, further correlations with demographics, immune response, or symptoms could not be performed.

**OTHER CMR ABNORMALITIES.** An abnormality was defined by either departmental standard clinical cut-points (e.g., aortic root 36 mm), laboratory test normal ranges (hsTnT <14 ng/l, NT-proBNP <400 pg/l), or for primary/secondary endpoints, by using the 75 seronegative subjects to define abnormal (2 SDs from mean: e.g., EF <54%, T<sub>1</sub> >1,072 ms, T<sub>2</sub> >52.4 ms). Mild abnormalities were found including: aortic root dilatation n = 2, all mild), LA dilatation (n = 6, all mild) reduced LV function (n = 2, EF 50%–53%); T<sub>1</sub> elevation

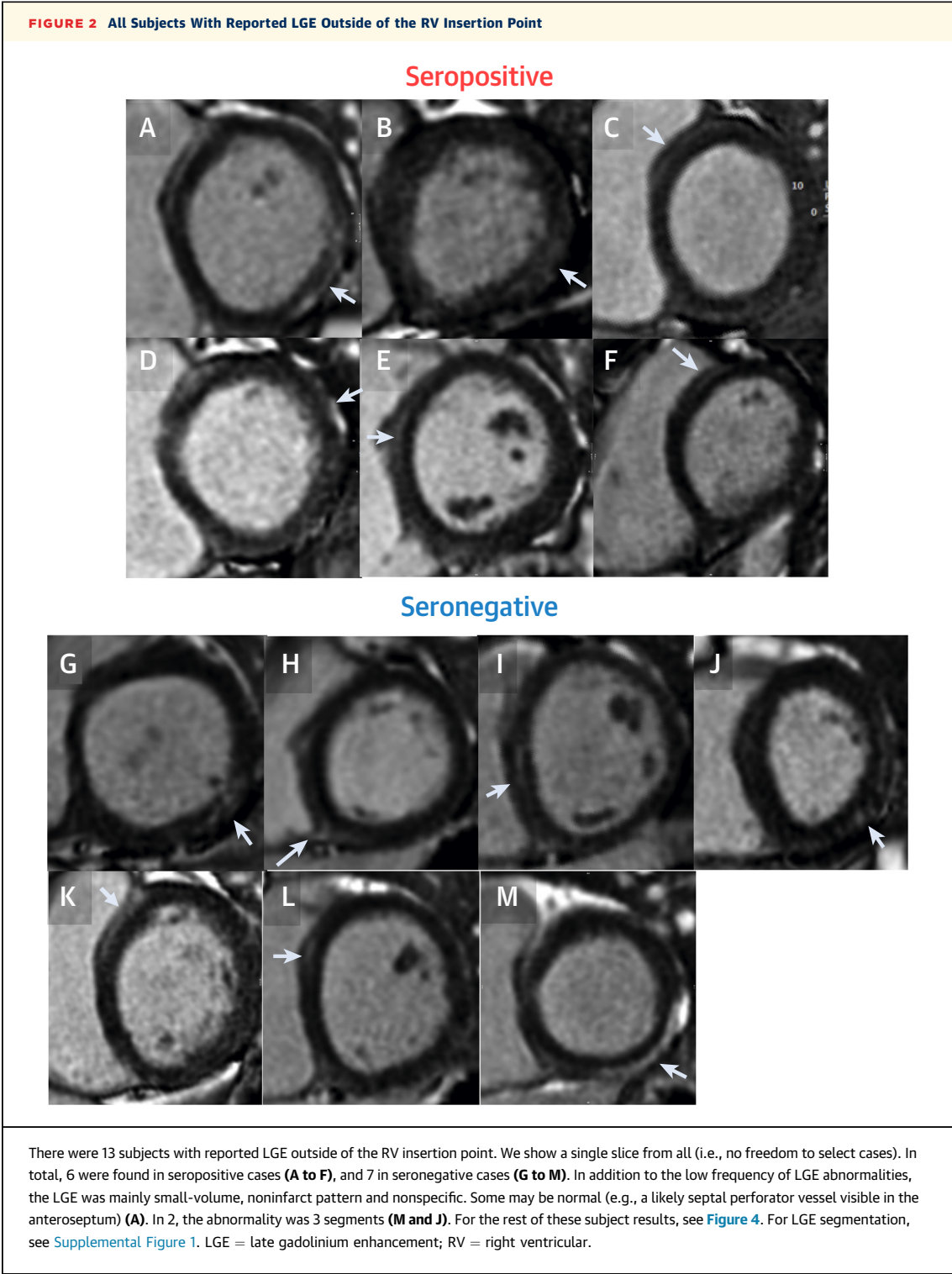


(n = 6), T<sub>2</sub> elevation (n = 9), non-RV insertion point LGE (n = 13, median 1%, maximum 5% of myocardium). All 13 cases with positive LGE are shown in [Figure 2](#) (6 were seropositive, 7 were seronegative; all were noninfarct pattern, and some of the LGE patterns were nonspecific [2 were 3 segments, 1 was 4 segments]). Prevalence of myocarditis-like scar was 4% both in the seropositive and seronegative groups (i.e., no significant difference). There was no pericardial thickening seen in any subject. Individual participant septal T<sub>1</sub> and T<sub>2</sub> data in both groups along with the other primary endpoints and global T<sub>1</sub> and T<sub>2</sub> are shown in [Figure 3](#). Note: there is a single T<sub>2</sub> septal outlier (4SD) that is considered on post hoc review to be erroneously high from poor motion correction, but has been left in the results. No

subject had NT-proBNP elevation. A total of 4 subjects had borderline troponin elevation (maximum 26 ng/l, 3 seronegative, 1 seropositive). None of these were statistically more common in the seropositive group. Clinical results review recommended 2 people to have notes/full study data review, further imaging (1 echocardiography for aortic valve review, 1 chest radiography—both required no further follow-up) and 4 underwent clinical review—2 for reduced LV function, 2 for noninfarct pattern LGE ([Figures 2J and 2M](#) [2M was found to have been chronic and unchanged since a healthy volunteer study in 2011]).

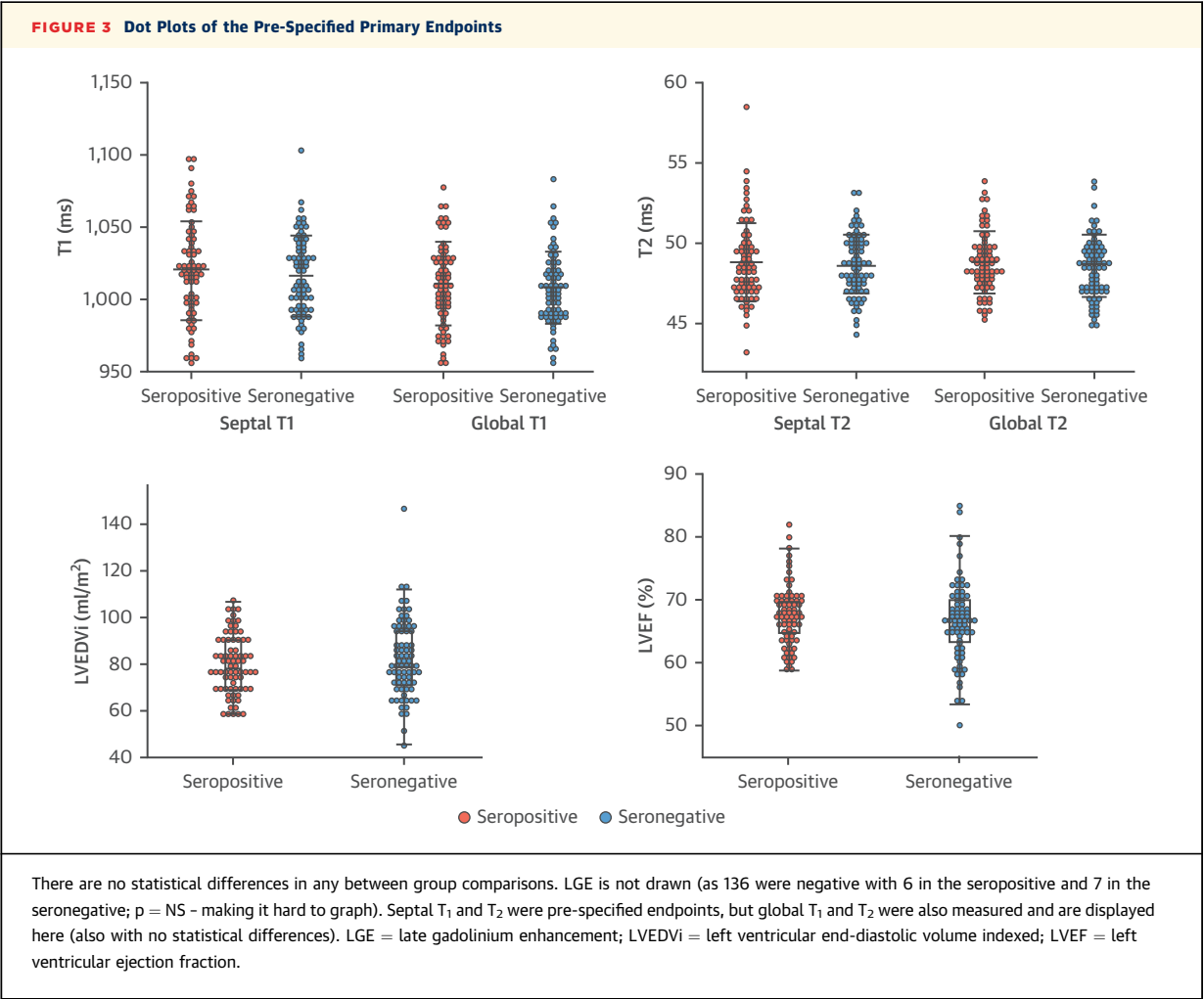
**ABNORMALITY CLUSTERING.** [Figure 4](#) shows results for all 149 subjects (rows) and across the 12 key biomarkers (10 primary/secondary imaging endpoints





plus blood biomarkers [columns]). Each horizontal row (12 across) is a health care worker split by serostatus (right/left) and in age order (top/bottom), for a total of 1,776 results. A green cell is a normal result; amber 2SDs abnormal, LGE present or biomarker

above lab reference range cut-off; red 4 SDs abnormal or LGE  $\geq 3$  segments; and white is missing data. LGE subjects are marked with the letters a to m cross-referencing [Figure 3](#), but only 2 participants (both seronegative) had LGE that looked clinically



significant. A disease phenotype is likely to have multiple abnormalities cosegregating within individual patients in a horizontal line, as was found in 1 subject (seronegative subject, age >55 years) (Figure 4). There were more individual seropositive participants with isolated values for septal T<sub>1</sub> and septal T<sub>2</sub> outside of 2 SDs from the mean than for seronegative participants, but these differences were nonsignificant, they did not cosegregate with LGE, and elevated values were not reproduced with global rather than septal measurement (Table 2) or with T<sub>1</sub> and T<sub>2</sub> as a continuous variable (Figure 2).

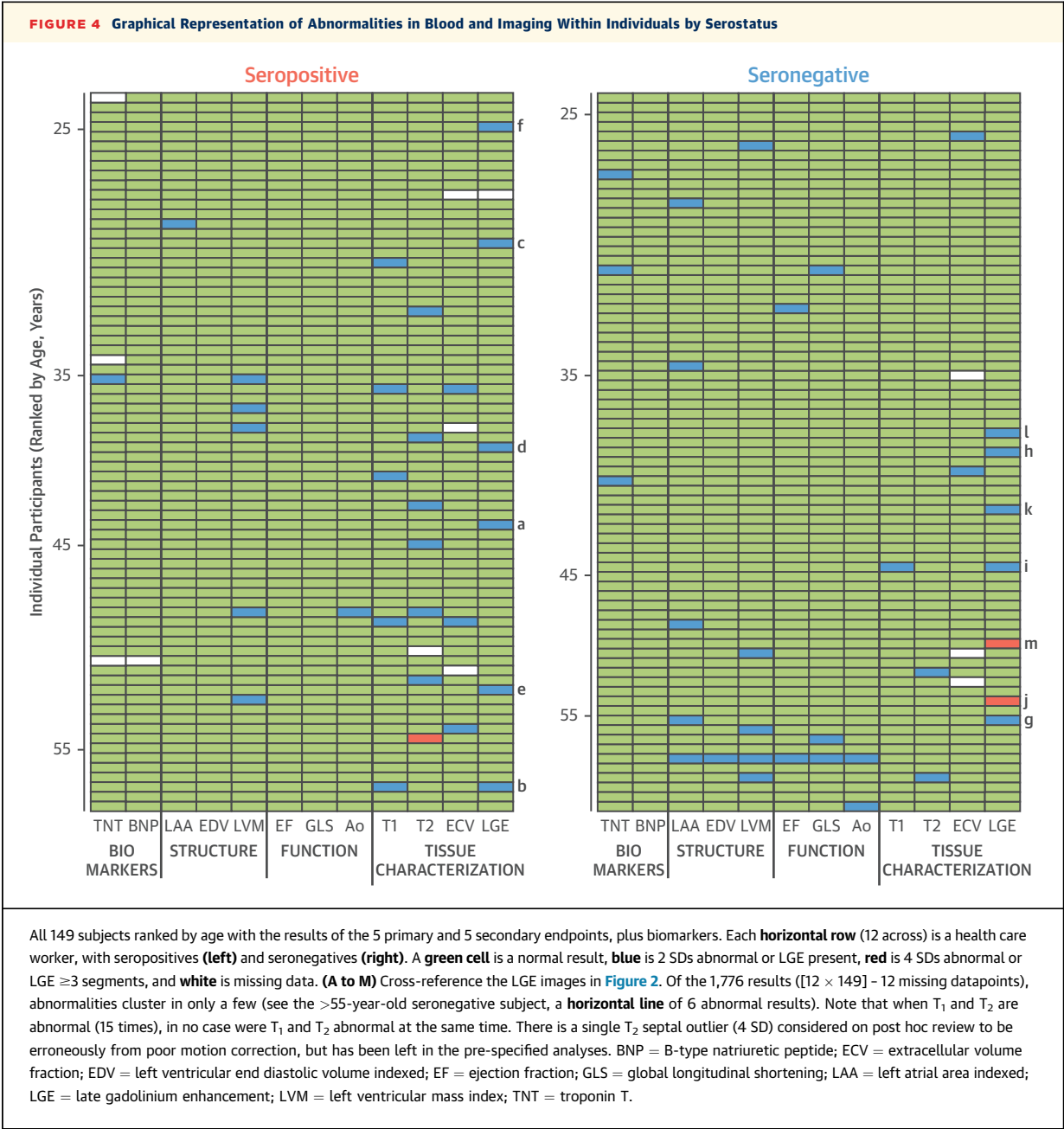
DISCUSSION

This study demonstrates that in healthy people, measured cardiovascular abnormalities are common, but no more common in those who had had mild SARS-CoV-2 6 months previously compared with those who had not. In other words, in this population,

mild COVID-19 left no measurable cardiovascular impact on LV structure, function, scar burden, aortic stiffness, or serum biomarkers. The cardiovascular phenotyping employed was comprehensive and measured parameters that reflected cardiac structure (LV volumes, mass, LA area), function (LVEF, global longitudinal shortening, mitral annular plane systolic excursion), inflammation (T<sub>1</sub> and T<sub>2</sub>), focal fibrosis (LGE), diffuse fibrosis (ECV), aortic compliance, heart rate, blood pressure, and high-sensitivity troponin and NT-proBNP.

The study was designed to focus on late effects after mild (rather than hospitalized) disease, following an earlier pathfinder study (14) that indicated high (78%) rates of post COVID-19 cardiac involvement with ongoing myocardial inflammation in 60%, even after nonhospitalized disease, based on mapping and late gadolinium enhancement findings. Subsequent studies have generally been small and included either convalescent symptomatic patients





(27), post-hospitalized patients (28), or specific populations (recovering athletes) (29). These results have collectively attracted widespread attention, with mainstream media coverage and downstream societal impact. Clinicians and experts managing viral myocarditis patients have queried the atypical duration of disease and rates of involvement with mild disease. In line with this, where histology is available from autopsy, meta-analyses have only occasionally shown lymphocytic infiltrates suggestive of myocarditis (30,31), but have more commonly found interstitial macrophage infiltration, consistent with other

forms of sepsis. In parallel, there has been discussion across several stakeholder groups recognizing limitations and differences between the design and technical methodology and analysis of some studies (32). Studies have generally included only severe disease or mixed populations without inclusion of asymptomatic seroconverters, and have scanned early following disease or at variable time points, meaning it is challenging to draw clear conclusions. Technical limitations include also include the T<sub>1</sub> mapping sequence used (high read-out flip angle rendering it prone to confounding by T<sub>2</sub>, heart rate,

off resonance, and magnetization transfer) (33) and the use of historic controls –time, sequence, scanner, institution, observer, and analysis method affect  $T_1$  measurement.

The current study has a number of advantages and was designed to address the knowledge gaps arising from prior studies. As a nested substudy of COVIDsortium, participants were prospectively recruited predominantly prior to infection, hence minimizing recruitment bias. This enabled identification of asymptomatic individuals with the mildest phenotype of disease who have not previously been studied for cardiovascular effects. Bias from symptom recall was low, and serological testing was comprehensive due to the parent study design with serial testing at a median of 10 time points using 2 assays. Control subjects were recruited from the same study contemporaneously, and were well matched with cases. The substudy recruited ~50% of seropositive individuals and matched control subjects. Scanning of case and control subjects was performed in parallel, and all acquisitions and analysis was performed blinded to serostatus. Quality control of  $T_1$  and  $T_2$  measurement was performed via U.S. Food and Drug Administration- and European Medicines Agency-approved phantom calibration showing near identical measurement performance and no temporal drift during the study. Application of validated AI analytic tools improves the ability to detect normal (23,24). New quality assurance methods were used including field map measurement in a subset and blinded review for region of interest identification by 2 separate U.S. based teams and review of  $T_1$  SD maps to validate performance (34). All analyses were pre-specified, and all images and metadata are available on reasonable request.

**STUDY LIMITATIONS.** The current study provides insight only into the short- to medium-term sequelae of community COVID-19 in workforce representative subjects age 18 to 69 years with low levels of comorbidities, and not the cardiovascular effects post-severe hospitalized infection or in those with multimorbidity. It does not prove that apparently mild SARS-CoV-2 never causes chronic myocarditis. The study design would not distinguish between individuals who had sustained completely healed myocarditis and pericarditis and those in whom the heart had never been affected; a cross-sectional athlete study at 1 month post-mild community COVID-19 reported a significant pericardial involvement (late enhancement and/or pericardial effusion), but this study is at 6 months (when the pericardium was normal). No baseline pre-COVID-19 imaging was

performed (35). We did not analyze other cardiovascular measures (including exercise testing). It would not be feasible or appropriate to obtain histological data from otherwise healthy subjects.

## CONCLUSIONS

In a workforce representative population, using best-available study design (prospective recruitment, contemporaneous control subjects, phantom scanner calibration, blinded analysis, full data availability to other researchers), there are no detectable persistent cardiovascular abnormalities 6 months post-mild infection with SARS-CoV-2 compared with matched case control subjects. Thus, screening in asymptomatic patients following nonhospitalized COVID-19 is currently not indicated.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Mild SARS-CoV-2 infection has not been found to cause detectable cardiovascular abnormalities 6 months post-infection in our study.

**COMPETENCY IN PATIENT CARE:** Our study provides societal reassurance for the cardiovascular health of working-age individuals with convalescence from mild SARS-CoV-2. Screening asymptomatic individuals following mild diseases is not indicated.

**COMPETENCY IN INTERPERSONAL AND COMMUNICATION SKILLS:** It is important to reassure

patients with mild SARS-CoV-2 infection regarding its cardiovascular effects.

**TRANSLATIONAL OUTLOOK:** Efforts to understand cardiovascular injury from SARS-CoV-2 infection require meticulous attention to study design, including inclusion of contemporary control groups and measurement quality control. This study suggests such research should focus on patients with acute infections or following severe hospitalized disease, with little benefit from screening asymptomatic patients following mild community infection.

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**KEY WORDS** cardiovascular magnetic resonance, COVID-19, late gadolinium enhancement, myocardial edema, myocarditis, SARS-CoV-2, troponin

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**APPENDIX** For an expanded Methods section and supplemental figures, please see the online version of this paper.